Editorial

Administration of influenza vaccines to patients with egg allergy

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Key words: *Egg allergy, influenza vaccine, ovalbumin*

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Patients who have generated IgE antibodies to an allergen are at risk for anaphylaxis with systemic exposure to that allergen. Thus patients who have IgE-mediated egg allergy are at risk for anaphylaxis if injected with influenza vaccines containing egg protein. Published studies, however, suggest that this risk is actually quite small, likely because of the very low quantity of ovalbumin in influenza vaccines, and that with appropriate precautions, influenza vaccine can be safely administered, even to patients with severe egg allergy. Egg allergy is relatively common among candidates for influenza vaccination because target groups for the vaccine include those with higher rates of egg allergy, specifically all children and young adults (from 6 months through 18 years for seasonal influenza and from 6 months through 24 years for H1N1 influenza) and all patients with asthma. Of note, the intranasal vaccines are not recommended for children with asthma, and a large percentage of children with egg allergy have asthma.

HOW FREQUENT AND SEVERE ARE ALLERGIC REACTIONS TO INFLUENZA VACCINES?

Anaphylactic reactions to influenza vaccines are exceedingly rare; however, it must be acknowledged that patients with egg allergy are typically excluded from influenza vaccination, which could account for the low rate of reported reactions. In 1976, the Center for Disease Control and Prevention coordinated nationwide surveillance for illnesses after influenza vaccination. Only 11 cases of anaphylaxis were reported out of 48,161,019 persons immunized (1 case per every 4.4 million vaccinees), and none of the 11 reported egg allergy.[1] An active surveillance system (Vaccine Safety Datalink) found no cases of anaphylaxis after the administration of 197,964 doses of influenza vaccine and estimated the risk per million doses administered to have a 95% CI of 0 to 18.6.[2] There is only a single report ever of a death (in 1969) from an anaphylactic reaction to an influenza vaccine in a patient with egg allergy, and the report is anecdotal, without details or investigation.[3] From 1990 to 2005, an estimated 747 million doses of influenza vaccine were administered in the United States.[4] A review of all reports to the Vaccine Adverse Event Reporting System over this 15-year period revealed 4 reports of deaths shortly after influenza vaccination that identified anaphylaxis as the cause.[4] The report provides neither information on egg allergy nor any evaluation to determine whether these were allergic reactions. By comparison, an estimated 540,000 deaths occurred over the same 15-year period from seasonal influenza disease, many of which could have been prevented by vaccination.[5] If only one half of 1% of these patients have egg allergy,[6] these preventable deaths might include hundreds of patients not vaccinated because they have egg allergy.

WHAT DO PUBLISHED STUDIES SAY ABOUT THE SAFETY OF ADMINISTERING INFLUENZA VACCINES TO PATIENTS WITH EGG ALLERGY?

James et al[7] administered influenza vaccine to 83 children and adults with egg allergy (median age, 3 years; range, 1-46 years) and 124 control subjects without egg allergy. The group with egg allergy all had positive egg skin test results and convincing histories of clinical reactions or positive blinded challenge results to egg, including 27 patients with "a convincing history of anaphylaxis including generalized urticaria, wheezing, laryngeal edema, and/or hypotension." Only 4 of the patients with egg allergy, as well as one of the control subjects without egg allergy, had a positive skin prick test result to full-strength influenza vaccine. Irrespective of skin test results, patients with egg allergy were given 10% of the dose of vaccine (0.025 mL or 0.05 mL depending on age) and observed for 30 minutes. If this portion of the dose was tolerated, the remaining 90% of the dose was given (0.225 or 0.45 mL), and patients were observed for an additional 60 minutes. Only 3 of the 83 patients with egg allergy had any reaction to the 10% dose (1 with mild throat itching, cough, and wheeze and 2 with a small hive); all resolved without treatment by 30 minutes, and all were given the remaining 90% dose without further reaction. Thirty-four children with egg allergy received booster doses of the same vaccine 1 month after the 2-dose protocol as a single dose without any adverse reaction. The investigators also assayed the ovalbumin content of the vaccines used in the study and found them to have 1.2 μg/mL or less. They also assayed other available brands of influenza vaccine (available in the same years as the study but not administered in the study) and found them to have ovalbumin contents as high as 42 μg/mL. From this study, it is clear that even patients with severe egg allergy can likely tolerate immunization with influenza vaccines containing 1.2 μg/mL ovalbumin or less. The authors calculated the 95% CI for the percentage of patients with egg allergy who can safely receive this vaccine as 95.7% to 100% (indicating that if this vaccine were administered to a larger number of patients with egg allergy, more cases of anaphylaxis could occur). Furthermore, given the fact that all 83 patients with egg allergy ultimately tolerated the 90% dose and that 34 subsequently tolerated the vaccine given as a single

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Disclosure of potential conflict of interest: J. M. Kelso has declared that he has no conflict of interest.

Received for publication December 11, 2009; revised February 10, 2010; accepted for publication February 16, 2010.

Available online March 12, 2010.

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J Allergy Clin Immunol 2010;125:800-2.

0091-6749/$36.00

doi:10.1016/j.jaci.2010.02.013

TABLE I. Approved influenza vaccines: United States, 2009-2010 season

Manufacturer/ distributor	Vaccine	Trade name	Route	How supplied	Age group	Stated ovalbumin content*
CSL Behring	Trivalent (inactivated) influenza vaccine (TIV)	Afluria	Intramuscular	0.25-mL prefilled syringe	6-35 mo	<0.5 μg per 0.25-mL dose
				0.5-mL prefilled syringe	≥36 mo	<1 μg per 0.5-mL dose
				5.0-mL multidose vial	†	
	Influenza A (H1N1) 2009 monovalent vaccine	No trade name	Intramuscular	0.25-mL prefilled syringe	6-35 mo	<0.5 μg per 0.25-mL dose
				0.5-mL prefilled syringe	≥36 mo	<1 μg per 0.5-mL dose
				5.0-mL multidose vial	†	
GlaxoSmithKline	Trivalent (inactivated) influenza vaccine (TIV)	Fluarix	Intramuscular	0.5-mL prefilled syringe	≥36 mo	<1 μg per 0.5-mL dose
		FluLaval	Intramuscular	5.0-mL multidose vial	≥18 y	
	Influenza A (H1N1) 2009 monovalent vaccine	No trade name	Intramuscular	10.0-mL multidose vial	≥18 y	
MedImmune	Live, attenuated influenza vaccine (LAIV)	FluMist	Intranasal	0.2-mL sprayer	2-49 y	<0.24 μg per 0.2-mL dose
	Influenza A (H1N1) 2009 live, attenuated influenza vaccine	No trade name				
Novartis	Trivalent (inactivated) influenza vaccine (TIV)	Fluvirin	Intramuscular	0.5-mL prefilled syringe	≥4 y	<1 μg per 0.5-mL dose
				5.0-mL multidose vial	†	
		Agriflu	Intramuscular	0.5-mL prefilled syringe	≥18 y	<0.4 μg per 0.5-mL dose
	Influenza A (H1N1) 2009 monovalent vaccine	No trade name	Intramuscular	0.5-mL prefilled syringe	≥4 y	<1 μg per 0.5-mL dose
				5.0-mL multidose vial	†	
Sanofi Pasteur	Trivalent (inactivated) influenza vaccine (TIV)	Fluzone	Intramuscular	0.25-mL prefilled syringe	6-35 mo	<2.5 μg per 0.25-mL dose
				0.5-mL prefilled syringe	≥36 mo	<5 μg per 0.5-mL dose
				0.5-mL single dose vial		
				5.0-mL multidose vial	*	
	Influenza A (H1N1) 2009 monovalent vaccine	No trade name	Intramuscular	0.25-mL prefilled syringe	6-35 mo	<2.5 μg per 0.25-mL dose
				0.5-mL prefilled syringe	≥36 mo	<5 μg per 0.5-mL dose
				0.5 mL single dose vial		
				5.0 mL multidose vial	†	

*All are as stated in package inserts except MedImmune and Sanofi Pasteur (personal communications).
†Multidose vials contain thimerosal as a preservative. Some state laws prohibit the administration of thimerosal-containing vaccines to young children and pregnant women.

(100%) booster dose, the authors comment that "Administration of the vaccine in 2 doses may be no different than administration of a single dose, when the content of egg protein in the vaccine preparation can be reliably determined."

HOW MUCH EGG PROTEIN IS IN INFLUENZA VACCINES?

Influenza vaccine might contain several egg white proteins, including ovomucoid, ovalbumin, and conalbumin. Manufacturers and independent research laboratories report ovalbumin content because ELISA assays are available to measure ovalbumin and ovalbumin reflects the amount of egg white protein in the vaccine. At the time the James et al study[7] was published in 1998, influenza vaccine manufacturers did not state the ovalbumin content of their vaccines. More recently, all but 1 manufacturer of these vaccines do provide this information in package inserts, and the 1 manufacturer that does not will provide the information by personal communication (Table I). The ovalbumin content of the vaccines in Table I is described in micrograms per dose because this is ultimately the amount of ovalbumin to which the patient is exposed. In the James et al study,[7] the maximum ovalbumin content of 1.2 μg/mL would translate to 0.6 μg per 0.5-mL dose or 0.3 μg per 0.25-mL dose. Thus influenza vaccines manufactured by CSL Biotherapies Inc (King of Prussia, Pa), GlaxoSmithKline (Research Triangle Park, NC), MedImmune, LLC (Gaithersburg, Md), and Novartis Vaccines and Diagnostics, Inc (Cambridge, Mass) all are reported to contain ovalbumin in amounts only slightly higher than the vaccines uneventfully administered to patients with egg allergy in the James et al study. The influenza vaccines manufactured by Sanofi Pasteur Inc (Swiftwater, Pa) are reported to contain up to 5 times higher amounts but are still well below the highest amounts measured in some influenza vaccines assayed but not administered in the James et al study.

In 2 recent studies[8,9] independent investigators assayed several brands and lots of seasonal and H1N1 influenza vaccines for the 2009-2010 season for ovalbumin content. The actual ovalbumin content of the tested vaccines was considerably (1 or 2 orders of magnitude) lower than the manufacturers' stated maximum levels.

ARE THERE PUBLISHED PROTOCOLS ON HOW TO ADMINISTER INFLUENZA VACCINE TO PATIENTS WITH EGG ALLERGY?

A number of published studies have advocated various approaches to the administration of influenza vaccines in patients

with egg allergy.[7,10-13] Some involve skin testing with the vaccine (skin prick testing at full strength with or without subsequent intradermal testing with the vaccine diluted 1:100). Based on the results of the skin testing, the vaccine is either withheld or administered in divided doses. Some involve administration of the vaccine as a single dose, whereas others advocate a 2-dose (10%/90% as above) or multidose protocol (for a 0.5-mL dose at 15-minute intervals: 0.05 mL of a 1:10 dilution, 0.05 mL of full-strength dose, 0.1 mL of full-strength dose, 0.15 mL of full-strength dose, 0.20 mL of full-strength dose). Finally, the protocols call for a waiting period of 15 to 30 minutes between doses and a 30- to 60-minute waiting period after the final dose. These recommendations were made at a time (or echo recommendations made at a time) when influenza vaccine package inserts did not state and vaccine manufacturers would not provide the ovalbumin content of the vaccines, and independent laboratories determined amounts to be up to 42 μg/mL. Now the package inserts for all but 1 vaccine state the content to be less than 1 μg per 0.5-mL dose, and independent laboratory investigations suggest the actual content is even lower.

IS IT TIME FOR A LESS CONSERVATIVE APPROACH?

Although skin testing is an appropriate method to evaluate allergic reactions to vaccines,[14] it might not be required in the specific case of administering influenza vaccines to patients with egg allergy. Such patients have a history of reacting to the ingestion of eggs, which should be confirmed by means of skin testing or *in vitro* assay for specific IgE antibody to egg at the time of influenza vaccination to see whether the egg allergy has resolved. However, such patients typically have no history of actually reacting to influenza vaccines. In the James et al study,[7] only 4 of 83 patients with egg allergy had positive vaccine skin test results (as did 1 of the control subjects without egg allergy), and all received the vaccine uneventfully. Other studies have also demonstrated some level of clinically irrelevant positive influenza vaccine skin test results.[12] Thus given the tolerability of vaccines with low ovalbumin content in patients with egg allergy irrespective of skin test results, routinely skin testing patients with egg allergy before the administration of influenza vaccines would seem not to be required. If a patient has had a previous reaction to an influenza vaccination itself, skin testing would still be appropriate because there are constituents of the vaccine other than egg that might have been responsible for the reaction.

When immunizing a patient with egg allergy with an influenza vaccine, it seems prudent to choose a vaccine with low ovalbumin content (Table I). In some cases the available vaccine with the lowest ovalbumin content might not be approved for the age group of a child with egg allergy to be vaccinated. In such cases consideration can be given to administering the lower ovalbumin vaccine "off label" because there is no reason to believe such vaccines would be unsafe or ineffective when administered outside their approved age ranges. (As a separate issue, multidose vials contain thimerosal as a preservative, and some state laws prohibit the administration of thimerosal-containing vaccines to young children and pregnant women.) Vaccines containing less than 1 μg of ovalbumin per 0.5-mL dose will almost certainly be well tolerated when administered as a single dose without prior vaccine skin testing. The evidence for this is the James et al study,[7] in which 90% or 100% of a dose of influenza vaccine containing 0.6 μg of ovalbumin per 0.5-mL dose (0.54 or 0.6 μg) was administered uneventfully to patients with egg allergy irrespective of vaccine skin test results. Nonetheless, the vaccine should be administered in a setting in which personnel and equipment are available to recognize and treat anaphylaxis, and patients should be observed for at least 30 minutes afterward. In patients with histories of severe reactions to egg or if only the higher ovalbumin influenza vaccines are available, additional precautions have been recommended as above.[7,10,12] This would include skin testing with the vaccine, skin prick tests at full strength with or without intradermal tests diluted 1:100, and, if the results of such skin tests were positive, administering the vaccine in the 2-dose or multidose protocol described above. The intranasal influenza vaccines represent the lowest ovalbumin exposure to patients with egg allergy; however, the exposure is through the nasal mucosa rather than intramuscular injection. Whether this would have any effect on the absorption and reaction to the allergen is unknown. Anaphylaxis has been reported after administration of intranasal influenza vaccine, although not directly linked to egg allergy.[12]

EDITORIAL OPINION

Patients with egg allergy for whom influenza vaccine is indicated can and should be vaccinated to decrease the morbidity and mortality associated with the disease. Based on available data, consideration can be given to administering a vaccine with a stated ovalbumin content of less than 1 μg per 0.5-mL dose (Table I) as a single dose without prior vaccine skin testing. Such immunization should take place in a setting in which personnel and equipment are available to recognize and treat anaphylaxis. Future studies are needed to validate this approach. When a low-ovalbumin vaccine is not available or in the case of more severe egg allergy, a more conservative approach might be warranted.

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